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Applicant(s) THOMAS P. PARKS, SAN MATEO, CA.

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TITLE
COMPOSITIONS AND METHODS OF TREATING ANORECTAL DISORDERS

DATA ENTRY BY: YON, LOWUAN TEAM: 05 DATE: 03/25/99

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PROVISIONAL APPLICATION

Docket No. 10692-005400
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Sir:

Transmitted herewith for filing is a provisional patent application under 37 CFR 1.53(c) of:

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY/STATE/COUNTRY)
Parks	Thomas	P.	San Mateo, California USA

Title: COMPOSITIONS AND METHODS OF TREATING ANORECTAL DISORDERS

Enclosed are:
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Respectfully submitted,

TOWNSEND and TOWNSEND and CREW LLP

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PATENT

Attorney Docket No. 010692-005400US

PROVISIONAL

PATENT APPLICATION

COMPOSITIONS AND METHODS OF TREATING ANORECTAL DISORDERS

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COMPOSITIONS AND METHODS OF TREATING ANORECTAL DISORDERS

DETAILED DESCRIPTION OF THE INVENTION

This invention is directed to compositions and methods for treating anorectal disorders such as anal fissures, anal ulcer, hemorrhoidal diseases and levator spasm by administering to an appropriate anal area of a subject (for example, the internal anal canal) in need of such treatment a spasmolytic agent which relaxes the internal anal sphincter muscle. More specifically, this invention describes the composition and methods for treating anorectal disorders with an agent which induces an increase in cyclic nucleotides in the anal sphincter muscle or mimics the actions of cyclic nucleotides in the affected anal sphincter muscle tissue, thereby reducing anal sphincter hypertonicity and/or spasm in patients afflicted with such disorders. This invention also relates to compositions comprising beta-adrenergic receptor antagonists and methods comprising administering to the appropriate anal area of a subject in need of such treatment (e.g., anal canal) a beta-adrenergic receptor antagonist to prevent the stimulatory neurogenic control, i.e. muscle contraction, thereby maintaining anal sphincter muscle relaxation.

In general, anal fissure (fissure-in-ano), anal ulcer, acute hemorrhoidal disease, and levator spasm (proctalgia fugax) are relatively common benign conditions of the anorectal area which affect subjects, including humans, of all ages, races, and sexes. However, these conditions can be problematical and inconvenient to treat and painful to endure. An anal fissure or ulcer is a tear or ulcer of the mucosa or lining tissue of the distal anal canal. An anal fissure or ulcer can be associated with another systemic or local disease, but is more frequently present as an isolated finding. The typical idiopathic fissure or ulcer is confined to the anal mucosa and usually lies in the posterior midline, distal to the dentate line. An individual with an anal fissure or ulcer frequently experiences anal pain and bleeding, the pain being more pronounced during and after bowel movements.

Hemorrhoids are specialized vascular areas lying subjacent to the anal mucosa. Symptomatic hemorrhoidal disease is manifest by bleeding, thrombosis and/or prolapse of the hemorrhoidal tissues. Commonly, internal hemorrhoidal tissue bulges into the anal canal during

defecation causing bleeding and pain. As the tissue enlarges, further bleeding and pain and prolapse and thrombosis can ensue. The thrombosis of hemorrhoids is another cause of bleeding and pain.

Levator spasm is a condition affecting women more frequently than men. This syndrome is characterized by spasticity of the levator ani muscle, a portion of the anal sphincter complex. The patient suffering from levator spasm may experience severe, episodic rectal pain. A physical exam may reveal spasm of the puborectalis muscle and pain may be reproduced by direct pressure on this muscle. Bleeding is normally not associated with this condition.

Sphincters are circular groups of smooth muscle that control the orifices of hollow organs. Sphincters present throughout the gastrointestinal (GI) tract control the passage of materials through this system of the body. When constricted, the sphincters close orifices leading to the hollow organs, such as the stomach, intestine, anus, etc. In order for the sphincter to open, the muscles must relax. The sphincter that closes the anus (sphincter ani) consists of two sphincter muscle groups. The external anal sphincter is a thin flat plane of striated muscle fibers adherent to the integument surrounding the margin of the anus. The internal anal sphincter (IAS) is a ring of smooth muscle which surrounds the lower extremity of the rectum and is formed by an aggregation of the involuntary circular fibers of the intestine. Inflammation locally may cause sphincter spasm and pain.

Anal sphincter spasm is a condition in which the muscles of the internal anal sphincter are under abnormal tension. The strong contractions of the internal anal sphincter associated with sphincter spasm often give rise to painful linear ulcers or crack-like sores, known as rectal fissures, on the margin of the anus. Anal sphincter spasm is also considered a cause of the pain following rectal surgery or thrombosed hemorrhoids. Current treatments of rectal fissures are directed at relieving sphincter spasm and include dilatation (under anesthesia) or cutting a part of the sphincter (lateral internal sphincterotomy). Applications of heat, cold, witch hazel, topical anesthetics, topical steroids, stool softeners, and bed rest have also been prescribed to treat rectal pain. However, none of these approaches significantly modifies the sphincter spasm itself.

A known moderator of sphincter tone is nitric oxide (NO). Nitric oxide has been shown to bring about a concentration-dependent reduction in the resting tension of internal sphincter smooth muscle strips *in vitro* (Rattan et al., Am. J. Physiol. 262:G107-112 (1992)), and

NO donors, e.g. nitroglycerin, isosorbide dinitrate, isosorbide mononitrate, reduce anal pressure in man (REF). NO has also been shown to mediate adaptive relaxation of other sphincters in the gastrointestinal tract including the lower esophageal sphincter (Conklin et al., Gastroenterology 104:1439-1444 (1993); Tottrup et al., Br. J. Pharmacol. 104:113-116 (1991)), pyloric sphincter (Bayguinov et al., Am. J. Physiol. 264:G975-983 (1993), sphincter of Oddi (Mourelle et al., Gastroenterology 105:1299-1305 (1993)), and the ileocolic sphincter (Ward et al., Br. J. Pharmacol. 105:776-782 (1992)). It is thought that NO or NO-like substances serve as important control mechanisms for the general phenomenon of gastrointestinal adaptive relaxation.

Anorectal disorders include diseases affecting the anorectal area of mammals, e.g. acute and benign anal fissures, internal and external hemorrhoidal diseases, etc. An anal fissure is a crack in the anal mucosa. Anal fissure is a relatively common and painful condition that affects humans of all ages, races, and sexes. Various therapies have been devised to treat anal fissures. The treatment of anal fissure has not changed for over 150 years; typically, non-surgical therapies include bulk laxatives and sitz baths. Approximately 60% of the acute anal fissure heal within three weeks under this treatment regimen. Acute anal fissures, which do not heal, become chronic anal fissures or anal ulcers. The hypertonicity of the internal anal sphincter muscle, which believed to be the main cause of anal fissures, can be relieved through surgical sphincterotomy. The Standards Task Force of the American Society of Colon and Rectal Surgeons recommends management of chronic anal fissures by "subcutaneous or open lateral internal sphincterotomy, posterior internal sphincterotomy with advanced flap, or manual dilatation"(REF). Healing occurs following sphincterotomy in 95% of cases. Successful sphincterotomy (or anal dilatation) is associated with a significant decrease in intra-anal pressure (REF). However, a number of patients experience incontinence following the surgical procedure. There is clearly a significant need for non-surgical treatments of anorectal disorders, including, for example, anal fissures and other anorectal conditions caused by anal sphincter spasm and or hypertonicity, including acute hemorrhoidal diseases and proctalgia fugax.

A promising new approach for treating anal disorders is the topical application of a nitric oxide donor, such as a nitrate, to an appropriate anal area. NO is an inhibitory neurotransmitter that moderates the tone of gastrointestinal sphincters, including the inner anal sphincter (IAS). Nitric oxide donors reduce maximal resting anal pressure and improve

anodermal blood flow. One problem associated with topical nitrate therapy, however, is the incidence of headache in the subjects to whom it is administered, particularly at high nitric oxide donor doses. A second problem pertaining to the use of nitric oxide donors is the possible development in the subject of drug tolerance -- a problem well documented for nitrate therapy in cardiovascular disease. An alternative pharmacological treatment of anorectal disorders (or a combination therapy comprising administering to the appropriate anal area of a subject in need of such treatment an organic nitric oxide donor with one or more other therapeutic compounds) complements the beneficial actions of organic nitric oxide donors (e.g., organic nitrates) while minimizing and/or eliminating adverse side effects.

NO donors, such as nitroglycerin (NTG), relax smooth muscle by stimulating the production of cyclic guanidine monophosphate (cGMP) which then activates cGMP-dependent protein kinase (PKG) (as determined by cardiovascular studies). Cyclic adenosine monophosphate (cAMP) also induces smooth muscle relaxation. We proposed that agents that elevate cyclic GNP or cyclic AMP levels or directly activate cyclic GMP-dependent protein kinase (PGA) or cyclic AMP-dependent protein kinase (PKA) may are thus therapeutically effective in relaxing anal sphincter muscle and reducing anal sphincter pressure. Other spasmolytic agents may also be effective in relieving muscle spasm associated with anorectal disorders.

There are various pharmacological agents that are known to affect the actions or levels of cAMP or cGMP in tissues other than anal sphincter muscles. These agents can be separated into three major pharmacological classes: 1) agents that stimulate an increase of either cGMP or cAMP through activation of guanylyl or adenylyl cyclases respectively, 2) agents that are cyclic nucleotide mimetics, and 3) agents that inhibit the breakdown of cGMP or cAMP. Among the first class of agents are, for example, beta-adrenergic receptor agonists, e.g. isoproterenol (ISO), salbutamol, etc. which are known to stimulate the level of tissue cAMP by binding specifically to the beta-adrenergic receptor located in the cellular membrane (Goodman & Gilman's "The Pharmacological Basis of Therapeutics", ninth edition, ed. JG Hardman, LE Limbird, PB Molinoff, RW Ruddon, and AG Gilman, McGraw-Hill Companies, 1996). Agents that directly activate Gs protein (stimulatory G protein), for example, cholera toxin, forskolin, and the like are also effective in inducing increase in cAMP. In the case of activating guanylyl cyclase, L-arginine, NO donors and atrial natriuretic factor (Neuser D, Bellemann P, Receptor

binding, cGMP stimulation and receptor desensitization by atrial natriuretic peptides in cultured A10 vascular smooth muscle cells. FEBS Lett 1986 Dec 15;209(2):347-51; Rambotti MG, Giambanco I, Spreca A, Detection of guanylate cyclases A and B stimulated by natriuretic peptides in gastrointestinal tract of rat. Histochem J 1997 Feb 29(2):117-26; Hampl V, Huang JM, Weir EK, Archer SL, Activation of the cGMP-dependent protein kinase mimics the stimulatory effect of nitric oxide and cGMP on calcium-gated potassium channels, Physiol Res, 44(1):39-44, 1995) and the like are all agents known to induce an increase in the tissue cGMP.

The second class of agents, i.e. inhibitors of phosphodiesterases (PDE), are agents which can block the breakdown of cAMP and cGMP in the tissue. PDE inhibitors include non-specific PDE inhibitors and specific PDE inhibitors. A non-specific PDE inhibitor inhibits more than one type of phosphodiesterase. A specific PDE inhibitor inhibits only one type of phosphodiesterase. Preferably, a specific PDE inhibitor inhibits only one type of phosphodiesterase with little, if any, effect on any other type of phosphodiesterase. Specific inhibitors of five cyclic nucleotide PDE isozyme families have been characterized: 8-methoxymethyl-IBMX(isobutyl methoxanthine) or vinpocetine (cyclic GMP-specific, calmodulin-dependent PDE type I), EHNA(erythro-9-(2-hydroxy-3-nonyl)adenine HCl) (cyclic GMP-stimulated PDE type II), milrinone (cyclic GMP-inhibited PDE type III), rolipram (cyclic AMP-specific PDE type IV), zaprinast (cyclic GMP-specific PDE type V, and Delpy E, le Monnier de Gouville, "Cardiovascular effects of a novel, potent and selective phosphodiesterase 5 inhibitor, DMPPO (1,3 dimethyl-6-(2-propoxy-5-methane sulphonylamidophenyl)-pyrazolo[3,4-d]pyrimidin-4-(5H)-one): *in vitro* and *in vivo* characterization." Br J Pharmacol 1996 Jul:118(6):1377-84), and IBMX (nonspecific PDE inhibitor). Current knowledge suggests that at least nine PDE isozyme forms exist -- with the most recently discovered one being type 9A (Fisher DA, Smith JF, Pillar JS, St Denis SH, and Cheng JB, "Isolation and Characterization of PDE9A, A Novel human cGMP-specific Phosphodiesterase", J. Biol. Chem, 273(25):15559-15564, 1998). Additionally, there are agents which are non-specific inhibitors of PDEs; such as, for example, IBMX, theophylline, aminophylline, caffeine, etc. (Vemulapalli S, Watkins RW, Chintala M, Davis H, Ahn HS, Fawzi A, Tulshian D, Chiu P, Chatterjee M, Lin CC, Sybertz EJ, "Antiplatelet and antiproliferative effects of SCH 51866, a novel type 1 and type 5 phosphodiesterase inhibitor." J Cardiovasc Pharmacol 1996, 28(6):862-9).

The third class of agents are compounds which "mimic" the action of either cGMP, cAMP or both, e.g., the 8-bromo and dibutyryl analogues of cyclic GMP and cyclic AMP, Sp-8-Bromo-cGMPS and 8-CPT cAMP, etc (Meyer RB and Miller JP, Analogs of cyclic AMP and cyclic GMP: general methods of synthesis and relationship of structure to enzyme activity. Life Sci 14(6):10119-1040, 1974; Hei YJ, MacDonell KL, McNeill JH, and Diamond J, Lack of correlation between activation of cyclic AMP-dependent protein kinase and inhibition of contraction of rat vas deferens by cyclic AMP analogs. Mol Pharmacol 39(2)233-238, 1991; Sandberg M, Butt E, Nolte C, Fischer L, Halbrugge M, Beltman J, Jahnsen T, Genieser HG, Jastorff B, and Walter U, Characterization of Sp-5,6-dichloro-1-beta-D-ribofuranosylbenzimidazole-3', 5'-monophosphorothioate (Sp-5,6-DCI-cBiMPS) as a potent and specific activator of cyclic-AMP-dependent protein kinase in cell extracts and intact cells. Biochem J 279(2):521-527, 1991; Meriney SD, Gray DB, and Pilar GR, Somatostatin-induced inhibition of neuronal Ca^{+2} current modulated by cGMP-dependent protein kinase, Nature 369:336-339, 1994).

All of these agents are useful in compositions for treating anorectal disorders and in methods for treating anal disorders utilizing such compositions. Since cyclic GMP and cyclic AMP relax smooth muscle through different mechanisms, an activator of both kinases should be especially efficacious in reducing anal pressure. These agents are useful in correcting or bypassing a defect in cyclic nucleotide production or accumulation by acting directly on the protein kinases that mediate the action of cyclic nucleotides.

Prevention of the release and function of the sympathetic neurotransmitters by administering to the appropriate anal are of a subject alpha-1-adrenergic receptor antagonists (i.e.α-blockers, e.g. prazosin, doxazosin, etc. Goodman & Gilman's "The Pharmacological Basis of Therapeutics", ninth edition, ed. JG Hardman, LE Limbird, PB Molinoff, RW Ruddon, and AG Gilman, McGraw-Hill Companies, 1996) or blocking adrenergic nerves (i.e., alpha-2-agonists, e.g. clonidine, norepinephrine depleters, e.g. guanethidine, bretylin, reserpine, etc. nerve destroyers, e.g. 6-hydroxy dopamine, norepinephrine synthesis inhibitors, e.g. alpha-methyl tyrosine, etc.) may also lead to anal sphincter relaxation and improve on the signs and ymptoms of anorectal disorders.

The fifth class of compound which are useful in relaxing anal sphincter muscles comprises potassium channel activators (i.e. potassium channel openers). ATP is thought to be

an inhibitory neurotransmitter released from enteric from non-adrenergic non-cholinergic nerves that relaxes gastric intestinal smooth muscle (Burnstock, G. Pharmacol. Rev. 24:509-81, 1972). ATP appears to act primarily by opening ATP-sensitive potassium (K+) channels which hyperpolarize the cell membrane, thus reducing calcium permeability and intracellular calcium concentrations, leading to relaxation. Synthetic compounds that activate ATP-sensitive K+ channels are believed to be smooth muscle relaxants. Selected ATP-sensitive potassium channel activators include minoxidil, pinocidil, minoxidil sulfate, diazoxide, levcromokalim, cromakalim, etc. (White R et al "Effect of Potassium Channel Openers on Relaxation to Nitric oxide and Endothelium-derived Hyperpolarizing Factor in Rat Mesenteric Artery". Eur J Pharmacol. 357(1):41-51, 1998). ATP-sensitive potassium channels are expressed GI smooth muscle (Koh et al. Biophys. J. 75:1793-80, 1998). Although the presence of ATP-sensitive potassium channels in internal anal sphincter muscle has not been identified, it is likely that specific potassium channel openers are useful in relaxing internal anal sphincter muscle and improving on the signs and symptoms of anorectal disorders.

While the effects of individual PDE inhibitors are sufficient to reduce anal pressure, PDE inhibitors can be combined for therapeutic treatment of anorectal disorders with NO donors, beta-adrenergic agonists, e.g. isoproterenol (ISO), or atrial natriurietic factor (ANF). The inhibition of the cyclic AMP degrading PDEs potentiates the efficacy of ISO, whereas inhibition of cyclic GMP specific PDE isozymes enhances the relaxant effects of NTG on the anal sphincter. If a particular PDE inhibitor, e.g. zaprinast, is particularly effective at reducing anal pressure or reducing the amount of NTG needed to reduce anal pressure, additional inhibitors of the class are also therapeutically effective (e.g. MY-5445, dipyridamole, sildenafil) in treating anorectal disorders. In addition, these agents may be given via the same route of administration (e.g., to the appropriate anal area or tissue or the external or internal anal canal) or can be given from two separate routes to maximize the therapeutic benefits of the treatment.

It has been shown that superoxide rapidly reacts with NO and dramatically reduces its biological effects. Conversely, the addition of exogenous superoxide dismutase (SOD) may enhance the effects of NO by scavenging superoxide. SOD is a very hardy enzyme and can be applied topically. It can, for example, be included in a NTG topical formulation to boost the local potency of NO generated from NTG. Note that the NO formed acts only locally due to its short half-life; in contrast, NTG is stable enough to exert systemic effects following

mucosal absorption. If SOD enhances the local efficacy of NTG, less NTG would be required to produce the same degree of internal anal sphincter relaxation, and less NTG would be absorbed to produce systemic effects.

The present invention provides composition of pharmacological agents of the classes defined above (including spasmolytic agents) and methods of treating anorectal disorders (including those related to hypertonicity and/or spasm of the internal anal sphincter muscle, e.g. hemorrhoidal pain, anal fissures, and for spasms of the mammal, especially the human, at the anorectal region) which comprise administering to the appropriate anal area of a subject in need of such treatment (e.g., internal or external anus or anal canal) composition comprising a pharmaceutically acceptable carrier and an effective amount of spasmolytic agent. In one aspect, this invention provides the composition comprising agents that induce elevated cyclic nucleotides in the anorectal tissue, thereby leading to the relief of anorectal hypertonicity and to the improvement in the signs and symptoms associated with anorectal disorders, e.g. anal fissures, anal ulcers and hemorrhoids) and methods of treating anorectal disorders comprising administering an effective amount of such composition to a subject in need of such treatment.

In another aspect, the present invention provides compositions for treating anorectal disorders which comprise a phosphodiesterase inhibitor, beta-adrenergic agonist, adenylyl cyclase activator, activator of guanylyl cyclase, and/or cyclic nucleotide mimetic--either alone, in any combination together with one another, or in combination with a nitric oxide donor or an analog of such nitric oxide donor. In another aspect, the present invention provides methods for treating anorectal disorders which comprise administering to the affected anal tissue or appropriate anal area (e.g., external or internal anal tissues or anal canal) a subject in need of such treatment a composition comprising a phosphodiesterase inhibitor, beta-adrenergic agonist, adenylyl cyclase activator, activator of guanylyl cyclase, and/or cyclic nucleotide mimetics--either alone or in combination together with one another or in combination with a nitric oxide donor or an analog of such nitric oxide donor.

This invention also provides compositions for treating an anorectal disorder comprising an effective amount of an α-adrenergic antagonist in a pharmaceutically acceptable carrier. In another aspect, the invention provides methods of treating anorectal disorders (including those related to hypertonicity and/or spasm of the internal anal sphincter muscle, e.g. hemorrhoidal pain and for spasms) of subjects, including mammals and human, which comprise

administering to an appropriate anal area of subject in need of such treatment (e.g., an affected internal or external anal tissue or internal or external anal canal) a composition comprising of agents that prevents the contraction of anal sphincter muscle, in pharmaceutically acceptable carrier systems. In one aspect, this invention provides compositions for treating anorectal disorders which comprise an amount of an α-adrenergic antagonist effective for the relief of anal disorders (e.g., anorectal hypertonicity and/or spasms) and for improvement of the signs and symptoms of associated with anorectal disorders, e.g. anal fissures, anal ulcers and hemorrhoids. The present invention also provides methods of treating anal disorders which comprise administering an effective amount of such compositions to the affected tissue or appropriate anal area (e.g., internal or external anal tissues or anal canal) of the subject in need of such treatment.

In another aspect, the present invention provides topical compositions useful for treating anorectal disorders (including those related to hypertonicity and/or spasm of the internal anal sphincter muscle, e.g. hemorrhoidal pain) and for treating spasms of the mammal, including humans, which comprise an effective amount of an agents that prevents the contraction of anal sphincter muscle and a pharmaceutically acceptable carrier systems. In one aspect, such agent is an ATP-sensitive potassium channel opener and a pharmaceutically acceptable carrier. In yet another aspect, the present invention provides methods for treating anal disorders which comprise administering to an appropriate anal area or affected anal tissue (e.g., external or internal anal tissue or anal canal) of a subject in need of such treatment an effective amount of such compositions comprising such agents (e.g., potassium channel openers). By use of such methods of the invention, anorectal hypertonicity and/or spasms are relieved and signs and symptoms associated with anorectal disorders, e.g. anal fissures, anal ulcers and hemorrhoids, are improved.

In another embodiment, the present invention provides topical pharmaceutical compositions in unit dosage form comprising per unit dosage an amount of a phosphodiesterase inhibitor, cyclic nucleotide mimic, or beta-adrenergic agonist effective for treating an anal disorder in a subject in need of such treatment in combination with a pharmaceutically acceptable carrier. Such compositions are useful in treating or reducing pain associated with anal disorders, such as hemorrhoidal pain, and for treating spasms and/or hypertonicity of the sphincters, including the internal anal sphincter, lower esophageal sphincter, pyloric sphincter, sphincter of Oddi, and the ileocolic sphincter. The topical composition is also useful in treating

conditions resulting from spasms and/or hypertonicity of sphincters of the anorectal region including anal fissure, post-operative rectal pain, hypertrophic pyloric stenosis, and pancreatitis, as well as conditions resulting from general spasm of the muscles of the GI tract including Zenkers diverticulum, achalasia, esophageal spasm (nutcracker esophagus), irritable bowel disease, and Hirshprungs disease (bowel obstruction). In yet another aspect, the present invention provides methods for treating anal disorders which comprise topically administering an effective amount of such compositions to an affected anal tissue or appropriate anal area of a subject in need of such treatment.

In still another embodiment, the invention provides pharmaceutical compositions in unit dosage form comprising per unit dosage a phosphodiesterase inhibitor, cyclic nucleotide mimetic, or beta-adrenergic agonist, and a pharmaceutically acceptable carrier; such compositions are useful for treating anal disorders, including those associated with hemorrhoidal pain, and for treating spasms and/or of the sphincters, including the internal anal sphincter, lower esophageal sphincter, pyloric sphincter, sphincter of Oddi, and the ileocolic sphincter. Such compositions may be administered orally. Such oral preparations are also useful in treating conditions resulting from spasms and/or hypertonicity of sphincters of the anorectal region including anal fissure, post-operative rectal pain, hypertrophic pyloric stenosis, and pancreatitis, as well as conditions resulting from general spasm of the muscles of the GI tract including Zenkers diverticulum, achalasia, esophageal spasm (nutcracker esophagus), irritable bowel disease, and Hirshprungs disease (bowel obstruction). In yet another aspect, the present invention provides methods for treating anal disorders which comprise orally administering an effective amount of such compositions to a subject in need of such treatment.

In another embodiment, this invention provides pharmaceutical compositions in unit dosage form comprising per unit dosage an effective amount of a phosphodiesterase inhibitor, cyclic nucleotide mimetic, or beta-adrenergic agonist, and a pharmaceutically acceptable parenteral dosage form as an effective treatment for a medical condition such as hemorrhoidal pain and for treating spasms of the sphincters including the internal anal sphincter, lower esophageal sphincter, pyloric sphincter, sphincter of Oddi, and the ileocolic sphincter. Such compositions may be administered parenterally. Such parenteral preparations are also useful in treating conditions resulting from spasms and/or hypertonicity of sphincters of the anorectal region including anal fissure, post-operative rectal pain, hypertrophic pyloric stenosis,

and pancreatitis, as well as conditions resulting from general spasm of the muscles of the GI tract including Zenkers diverticulum, achalasia, esophageal spasm (nutcracker esophagus), irritable bowel disease, and Hirshprungs disease (bowel obstruction). In another aspect, the present invention provides methods for treating anal disorders which comprise administering an effective amount of such composition parenterally to a subject in need of such treatment.

In yet another embodiment, this invention comprises the compositions comprising and methods of using the phosphodiesterase inhibitors, cyclic nucleotide mimetics or beta-adrenergic agonists in combinations with local anesthetic agents, for example lidocaine, prilocaine, etc. in a pharmaceutically acceptable dosage form as an effective treatment for a medical condition such as hemorrhoidal pain and for treating spasms and/or hypertonicity of the sphincters including the internal anal sphincter, lower esophageal sphincter, pyloric sphincter, sphincter of Oddi, and the ileocolic sphincter. These pharmaceutical preparations are also useful in treating conditions resulting from spasms and/or hypertonicity of sphincters of the anorectal region including anal fissure, post-operative rectal pain, hypertrophic pyloric stenosis, and pancreatitis, as well as conditions resulting from general spasm of the muscles of the GI tract including Zenkers diverticulum, achalasia, esophageal spasm (nutcracker esophagus), irritable bowel disease, and Hirshprungs disease (bowel obstruction). In another aspect, the present invention provides methods for treating anal disorders which comprise administering an effective amount of such composition along with a local anesthetic agent to a subject in need of such treatment. Such compositions can be administered orally, topically, or parenterally.

In yet another embodiment, this invention comprises the composition and methods of using the phosphodiesterase inhibitors, cyclic nucleotide mimetics or beta-adrenergic agonists in combinations with local anti-inflammatory agents, for example, naproxen, piroxicam, etc. in a pharmaceutically acceptable dosage form as an effective treatment for a medical condition such as hemorrhoidal pain and for treating hypertonicity and/or spasms of the sphincters including the internal anal sphincter, lower esophageal sphincter, pyloric sphincter, sphincter of Oddi, and the ileocolic sphincter. These pharmaceutical preparations are also useful in treating conditions resulting from spasms and/or hypertonicity of sphincters of the anorectal region including anal fissure, post-operative rectal pain, hypertrophic pyloric stenosis, and pancreatitis, as well as conditions resulting from general spasm of the muscles of the GI tract including Zenkers diverticulum, achalasia, esophageal spasm (nutcracker esophagus), irritable

bowel disease, and Hirshprungs disease (bowel obstruction). In another aspect, the present invention provides methods for treating anal disorders which comprise administering an effective amount of such composition along with a local anesthetic agent to a subject in need of such treatment. Such compositions can be administered orally, topically, or parenterally.

In yet another embodiment, the invention includes compositions for treating anal disorders which comprise a pharmaceutically acceptable carrier and an anal sphincter relaxing agent (e.g., a phosphodiesterase inhibitor, such as sildenafil) in an amount in the range of from approximately 0.01 to about 10 mg per 0.1 ml. The topical composition of an anal sphincter relaxing agent, e.g. a phosphodiesterase inhibitor such as sildenafil, can be applied directly to the appropriate anal area or affected area (such as the external or internal anus, anal sphincter, or anal canal). Depending on the concentration of the anal sphincter relaxing agent (e.g., a phosphodiesterase inhibitor, such as sildenafil) in the composition, application of the topical composition relieves hemorrhoidal pain and relaxes sphincter pressure in approximately 10 to 30 minutes.

The invention generally features a composition of and treatment for a medical conditions of the anorectal area and treatment of pain associated with such conditions (e.g., hemorrhoidal pain) and treatment of spasms and/or hypertonicity of the sphincters.

I. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which this invention belongs. The following references provide one of skill with a general definition of many of the terms used in this invention: Singleton et al., DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY (2d ed. 1994); THE CAMBRIDGE DICTIONARY OF SCIENCE AND TECHNOLOGY (Walker ed., 1988); and Hale & Marham, THE HARPER COLLINS DICTIONARY OF BIOLOGY (1991). As used herein, the following terms have the meanings ascribed to them unless specified otherwise. Although any methods and materials similar or equivalent to those described herein may be used in the practice or testing of the present invention, the preferred methods and materials are described. For purposes of the present invention, the following terms are defined below.

The term "spasmolytic agent" refers to an agent that can arrest a spasm and convulsion (PDR Medical Dictionary, by William Wood and Company, 1995). Spasmolytic agents are agents which increase the levels or actions of cyclic nucleotides. More specifically, spasmolytic agents are agents which increase the levels or actions of cyclic guanidine monophosphate or cyclic adenosine monophosphate.

The terms "treatment", "therapy" and the like include, but are not limited to, changes in the recipient's status. The changes can be either subjective or objective and can relate to features such as symptoms or signs of the disease or condition being treated. For example, if the patient notes decreased itching or decreased pain, then successful treatment has occurred. Similarly, if the clinician notes objective changes, such as by histological analysis of a biopsy sample, then treatment has also been successful. Alternatively, the clinician may note a decrease in the size of lesions or other abnormalities upon examination of the patient. This would also represent an improvement or a successful treatment. Prevention of deterioration of the recipient's status is also included by the term. Therapeutic benefit includes any of a number of subjective or objective factors indicating a response of the condition being treated as discussed herein. "Drug", "pharmacological agent", "pharmaceutical agent", "active agent", and "agent" are used interchangeably and are intended to have their broadest interpretation as to any therapeutically active substance which is delivered to a living organism to produce a desired, usually beneficial effect.

"Pharmaceutically- or therapeutically-acceptable" refers to a substance which does not interfere with the effectiveness or the biological activity of the active ingredients and which is not toxic to the hosts, which may be either humans or animals, to which it is administered. Therapeutically-effective amount" refers to the amount of an active agent sufficient to induce a desired biological result. That result may be alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. The term "therapeutically effective amount" is used herein to denote any amount of the topical formulation which causes a substantial improvement in a disease condition when applied to the affected areas repeatedly over a period of time. The amount will vary with the condition being treated, the stage of advancement of the condition, and the type and concentration of formulation applied. Appropriate amounts in any given instance will be readily apparent to those skilled in the art or capable of determination by routine experimentation.

The term "spasm" is defined herein to include any strong involuntary movement or muscular contraction lasting for a prolonged period. Spasm can be colonic (characterized by alternate contraction and relaxation) or tonic (sustained).

The term "anorectal area" is defined herein to include both the anus and the rectum region of a mammal.

"Hypertonicity" refers to being in state of greater than normal muscular tension or of incomplete relaxation.

The term "cyclic nucleotide" refers to cyclic adenosine monophosphate and cyclic guanosine monophosphate.

"cAMP" refers to cyclic adenosine monophosphate.

"cGMP" refers to cyclic guanosine monophosphate.

The term "modulation" refers any systematic variation or graded change in a characteristic (e.g. frequency, concentration, amplitude, effectiveness, etc.) of a sustained oscillation sufficient to affect a biological function. The term "change" includes an increase or decrease in the characteristic.

The term "subject" as used herein includes animal, such as a mammal, including a human.

The term "anorectal disorder" includes any disorder associated with an anal rectal disease, including an acute or chronic anal fissure, an internally or externally thrombosed

hemorrhoid, a hemorrhoidal disease, a disorder associated with endoscopic hemorrhoidal ligation or pain caused by such ligation, and other anorectal disorder caused by hypertonicity or spasm of the anal sphincter muscle.

The terms "potassium channel opener" and "potassium channel opener activity" refer generally to an increased flow of potassium ions from inside an electrically excitable cell to outside the cell via a membrane of the cell which has at least one potassium channel. Potassium channel opener activity may be observed by measuring an increase in the flow of potassium ions from inside a cell to outside the cell via a potassium channel in the cell membrane.

The term "pharmaceutical composition" means a composition suitable for pharmaceutical use in a subject, including an animal or human. A pharmaceutical composition generally comprises an effective amount of an active agent and a pharmaceutically acceptable carrier.

The term "pharmaceutically acceptable carrier" encompasses any of the standard pharmaceutical carriers, buffers and excipients, including phosphate-buffered saline solution, water, and emulsions (such as an oil/water or water/oil emulsion), and various types of wetting agents and/or adjuvants. Suitable pharmaceutical carriers and their formulations are described in REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Publishing Co., Easton, 19th ed. 1995). Preferred pharmaceutical carriers depend upon the intended mode of administration of the active agent. Typical modes of administration are described below.

The term "effective amount" means a dosage sufficient to produce a desired result. The desired result may comprise a subjective or objective improvement in the recipient of the dosage.

A "prophylactic treatment" is a treatment administered to a subject who does not exhibit signs of a disease or exhibits only early signs of a disease, wherein treatment is administered for the purpose of decreasing the risk of developing pathology.

A "therapeutic treatment" is a treatment administered to a subject who exhibits signs of pathology, wherein treatment is administered for the purpose of diminishing or eliminating those pathological signs.

The term "appropriate anal area" means any area or tissue of the anus or sphincter that is affected by or subject to anal disorder or disease, including, for example, the external or internal anus, the external or internal anal sphincter, anal sphincter muscle, or external or internal anal canal.

II. Dosage Forms and *In Vivo* Models

A) Dosage Forms

Dosage forms for the topical administration of the anal sphincter relaxing agents of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, suppositories and liposomal preparations. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants, which may be required. Topical preparations can be prepared by combining the anal sphincter relaxing agent with conventional pharmaceutical diluents and carriers commonly used in topical dry, liquid, cream and aerosol formulations. Ointment and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Such bases may include water and/or an oil such as liquid paraffin or a vegetable oil such as peanut oil or castor oil. Thickening agents which may be used according to the nature of the base include soft paraffin, aluminum stearate, cetostearyl alcohol, propylene glycol, polyethylene glycols, woolfat, hydrogenated lanolin, beeswax, and the like. Lotions may be formulated with an aqueous or oily base and, in general, also include one or more of the following: stabilizing agents, emulsifying agents, dispersing agents, suspending agents, thickening agents, coloring agents, perfumes, and the like. Powders may be formed with the aid of any suitable powder base, *e.g.*, talc, lactose, starch, and the like. Drops may be formulated with an aqueous base or non-aqueous base also comprising one or more dispersing agents, suspending agents, solubilizing agents, and the like.

The ointments, pastes, creams and gels also may contain excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof. Powders and sprays also can contain excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

In one aspect, the invention provides compositions for treating anorectal disorders which comprise an active agent and a pharmaceutically acceptable carrier. The active agent comprises a spasmolytic agent, which includes an agent that stimulate or causes an increase of either cGMP or cAMP through activation of guanylyl or adenylyl cyclase, respectively, a cyclic

nucleotide mimetic, PDE inhibitor, alpha-adrenergic receptor antagonist, or beta-adrenergic receptor agonist, or potassium channel opener. In one aspect, the active agent (e.g., spasmolytic agent) is present in compositions of the invention in an amount of from about 0.001% to about 15% by weight of the composition. In another aspect, the active agent (e.g., spasmolytic agent) is present in such compositions in an amount of from about 0.001% to about 15% by weight of the composition. In another aspect, the active agent (e.g., spasmolytic agent) is present in an amount of from about 0.01% to about 7.5% by weight or from about 0.05% to about 2% by weight of the composition.

For example, in one aspect, the invention provides compositions for treating anorectal disorders comprising a pharmaceutically acceptable carrier and an amount of from about 0.001% to about 15% sildenafil by weight. In another aspect, compositions comprising a pharmaceutically acceptable carrier and an amount of from about 0.01% to about 7.5% or from about 0.05% to about 2% sildenafil by weight are provided.

The topical pharmaceutical compositions can also include one or more preservatives or bacteriostatic agents, *e.g.*, methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chlorides, and the like. The topical pharmaceutical compositions also can contain other active ingredients such as antimicrobial agents, particularly antibiotics, anesthetics, analgesics, and antipruritic agents.

One example of a topical formulation includes 75% (w/w) white petrolatum USP, 4% (w/w) paraffin wax USP/NF, lanolin 14% (w/w), 2% sorbitan sesquioleate NF, 4% propylene glycol USP, and 1% anal sphincter relaxing agent.

The dosage of a specific anal sphincter relaxing agent depends upon many factors that are well known to those skilled in the art, for example, the particular agent; the condition being treated; the age, weight, and clinical condition of the recipient patient; and the experience and judgment of the clinician or practitioner administering the therapy. An effective amount of the compound is that which provides either subjective relief of symptoms or an objectively identifiable improvement as noted by the clinician or other qualified observer. The dosing range varies with the compound used, the route of administration and the potency of the particular compound.

Transmucosal (*i.e.*, sublingual, rectal, colonic, pulmonary, buccal and vaginal) drug delivery provides for an efficient entry of active substances to systemic circulation and

reduce immediate metabolism by the liver and intestinal wall flora (*See* Chien Y.W., NOVEL DRUG DELIVERY SYSTEMS, Chapter 4 "Mucosal Drug Delivery," Marcel Dekker, Inc. (1992). Transmucosal drug dosage forms (*e.g.*, tablet, suppository, ointment, gel, pessary, membrane, and powder) are typically held in contact with the mucosal membrane and disintegrate and/or dissolve rapidly to allow immediate local and systemic absorption. These formulations are used along with the anti-inflammatory agents of the present invention for reducing or eliminating inflammation of transmucosal membranes.

For delivery to the buccal membranes, typically an oral formulation, such as a lozenge, tablet, or capsule is be used. The method of manufacture of these formulations are known in the art, including but not limited to, the addition of a pharmacological agent to a pre-manufactured tablet; cold compression of an inert filler, a binder, and either a pharmacological agent or a substance containing the agent (as described in U.S. Patent No. 4,806,356); and encapsulation. Another oral formulation is one that can be applied with an adhesive, such as the cellulose derivative, hydroxypropyl cellulose, to the oral mucosa, for example as described in U.S. Pat. No. 4,940,587. This buccal adhesive formulation, when applied to the buccal mucosa, allows for controlled release of the pharmacological agent into the mouth and through the buccal mucosa. The anti-inflammatory agents of the present invention can be incorporated into these formulations as well.

For delivery to the nasal or bronchial membranes, typically an aerosol formulation is employed. The term "aerosol" includes any gas-borne suspended phase of the pharmacological agent which is capable of being inhaled into the bronchioles or nasal passages. Specifically, aerosol includes a gas-borne suspension of droplets of the compounds of the instant invention, as may be produced in a metered dose inhaler or nebulizer, or in a mist sprayer. Aerosol also includes a dry powder composition of a compound of the pharmacological agent suspended in air or other carrier gas, which may be delivered by insufflation from an inhaler device, for example. For solutions used in making aerosols, the preferred range of concentration of the pharmacological agent is 0.1-100 milligrams (mg)/ milliliter (mL), more preferably 0.1-30 mg/mL, and most preferably, 1-10 mg/mL. Usually the solutions are buffered with a physiologically compatible buffer such as phosphate or bicarbonate. The usual pH range is 5 to 9, preferably 6.5 to 7.8, and more preferably 7.0 to 7.6. Typically, sodium chloride is added to adjust the osmolarity to the physiological range, preferably within 10% of isotonic. Formulation

of such solutions for creating aerosol inhalants is discussed in Remington's Pharmaceutical Sciences, see also, Ganderton and Jones, DRUG DELIVERY TO THE RESPIRATORY TRACT, Ellis Horwood (1987); Gonda (1990) *Critical Reviews in Therapeutic Drug Carrier Systems* 6:273-313; and Raeburn *et al.* (1992) *J. Pharmacol. Toxicol. Methods* 27:143-159. Solutions of the pharmacological agent may be converted into aerosols by any of the known means routinely used for making aerosol inhalant pharmaceuticals. In general, such methods comprise pressurizing or providing a means of pressurizing a container of the solution, usually with an inert carrier gas, and passing the pressurized gas through a small orifice, thereby pulling droplets of the solution into the mouth and trachea of the animal to which the drug is to be administered. Typically, a mouthpiece is fitted to the outlet of the orifice to facilitate delivery into the mouth and trachea.

Solutions and aqueous suspensions are the pharmaceutical forms most widely used to administer drugs that must be active on the eye surface or in the eye after passage through the cornea or conjunctiva. To increase bioavailability of drugs, to extend therapeutic efficacy, and to improve patient compliance, various dosage forms have been developed over the years. These include soluble inserts (undergoing gradual dissolution/or surface erosion), insoluble inserts (*e.g.*, medicated contact lenses such as Ocusert®, etc.), gels (*e.g.*, Gelrite®), liposomal and drug delivery via nanoparticles (emulsion, suspension, etc.), and ointment (*See* Edman, BIOPHARMACEUTICS OF OCULAR DRUG DELIVERY, CRC Press, 1993).

B) *In Vivo Models*

Male Sprague-Dawley rats (300-400 gm are fasted 24 hours prior to anesthetization with ketamine (90 mg/kg), xylazine (9 mg/kg) given intramuscularly and supplemented as needed. Rats are placed on a heating pad for the duration of the experiments. The diuretic effects of anesthesia are offset by rehydration with saline through an intraperitoneal implanted 24 gauge angiocatheter (VWR, San Francisco, CA). The constriction/relaxation measurement assembly includes a 13F pediatric anorectal motility catheter (Synthetics Medical Inc., Irvine, CA) equipped with a small, water-filled, latex rubber balloon (LV #3, 3 mm diameter x 7 mm long; Kent Scientific Corp., Litchfield, CT). Resting pressure is measured after baseline stabilization using a Gould Stathem P23 ID pressure transducer over either 0-100 mm Hg, or 0-50 mm Hg ranges. Drug deliver is accomplished through two 250 µl syringes with no

dead space using PE 10 tubing inserted 3 mm and 7 mm into the anus, but proximal to the balloon. However, drug can also be applied orally or parenterally. The balloon and tubings are positioned in the anus using a small smooth-ended surgical forceps, as a speculum, to gently dilate the orifice. Drugs typically are applied one to one and one half hours after insertion of the instruments to allow establishment of a stable baseline. After application of the drug, regardless of the route of administration, the pressure of the anal sphincter is measured as a function of time. Drugs reduced the pressure are considered anal sphincter relaxing agents.

The present invention is further illustrated by the following examples. These examples are merely to illustrate aspects of the present invention and are not intended as limitations of this invention.

EXAMPLES

Example 1.

A composition of a base gel comprising 1.0 gram of salbutamol, 0.6 gm of carbopol 1342 USP, 35.44 gm of propylene glycol, 15.16 gm of dehydrated ethanol USP, 15.16 gm of isopropyl alcohol USP 2.5 % oleic acid, triethanolamine HCl 1N to adjust the pH from 6.0 to 7.0, 0.05 gm of butylated hydroxytoluene NF, and 29.72 gram of purified water USP. Other concentrations of salbutamol can be added in the same gel base to achieve the therapeutically effective dose; this can also be achieved by adjusting the concentration of other β-agonists with gel base excipients such as oleic acid.

Example 2.

One example of a topical composition comprises 0.05 to 1% sildenafil, 75% (w/w) white petrolatum USP, 4% (w/w) paraffin wax USP/NF, lanolin 14% (w/w), 2% sorbitan sesquioleate NF, and 4% propylene glycol USP at the therapeutic effective dose to the anorectal area. Typically, the 50 gm to 600 mg of sildenafil ointment can be applied to the anorectal area in order to relief the signs an/or symptoms associated with anorectal disorders, for example, anal fissure, anal ulcers, and hemorrhoidal diseases. The concentration of sildenafil, or other phosphodiesterase inhibitors can be varied by adjusting the ratio between the sildenafil with excipients facilitate either the attachment of sildenafil to the local tissue, or agents enhance absorption to the afflicted tissue.

Yet another example of a topical composition comprises nitroglycerin at 0.1% concentration and sildenafil at 0.1% concentration can be incorporated in the same ointment base as mentioned above. This composition can be applied topically from a metered dose devise where a 50 to 500 gm of the compositions is administered to the afflicted tissue at the anorectal area to achieve the desired therapeutic effects.

Another therapeutic regimen is to provide patients afflicted with the anorectal disorders with both oral sildenafil tablets and topical nitroglycerin ointment. These two dosage forms can be used in combinations which provide the best efficacy and compliance among these patients.

Example 3.

A composition of aminothylline topical spray composition comprises 0.1 to 5.0% (w/w) of aminothylline, acetylated lanolin alcohol, aloe vera, butane, cetyl acetate, hydrofluorocarbon, methyl paraben, PEG-8 laurate and polysorbate 80 in a 2 oz. pump spray bottle. The concentration of aminophylline or other non-specific phosphodiesterase inhibitors can vary between 0.5% to 5%. Other non-hydrofluorocarbon propellant can also be used instead of hydrofluorocarbon in the current composition. This composition can be sprayed directly onto the afflicted tissue once to four times daily to achieve the desired relief of signs and/or symptoms associated with anorectal disorders. This composition can also include menthol and benzocaine to provide the immediate local pain relief and soothing sensation whereas aminophylline provides the longer lasting relaxation of anal sphincter pressure.

Example 4.

A base cream composition comprises 2 gram prazosin hydrochloride (2.0 % w/w), 54.3 gm of purified water USP, 2 gm of Sepigel 305, 4.5 gram of Crodamol , 5.0 gm of glycerin, 6.0 gram sesame oil, 15.0 gram of white petrolatum USP, 2.0 gm of lanolin USP, 7.0 gram of 1,3-butylene glycol, 0.2 gm of methylparaben and 2.0 gm of silicon HL88.

A base cream can be prepared by first separate mixings of aqueous versus non-aqueous, i.e. oil phase, components of the cream. Once the aqueous phase containing the prazosin hydrochloride is well mixed, the melted oil phase is gently stirred into the aqueous phase to form a uniform cream base.

Example 5.

Sildenafil, a specific inhibitor of type V phosphodiesterase, can be given either orally via a tablet, parenterally or can be applied to patients diagnosed with anal fissures, either acute or chronic anal fissures, or other anorectal disorders. Sildenafil can be given one to three times daily for 8 weeks, especially in the case of patients afflicted with chronic anal fissure to cause the reduction of signs and symptoms associated with anorectal disorders.

For topical application, an approximate 50 mg to 900 mg of the cream measured by a metered dose devise, containing sildenafil, at the concentration from 0.02% to 5%, can be applied to the afflicted anorectal region using an application or by finger, one to four times daily

to achieve the desirable therapeutic effects. Alternatively, the oral and topical treatment can be used in a defined regimen to achieve the best therapeutic effects.

Example 6.

A phosphodiesterase inhibitor, for example aminophylline, can be given either orally via a tablet, parenterally or can be applied to patients diagnosed with anal fissures or other anorectal disorders, either acute or chronic anal fissures from a topical dosage form, e.g. a cream. For topical application, an approximate 50 mg to 900 mg of the cream measured by a metered dose devise, can be applied to the afflicted anorectal region using an application or by finger, one to four times daily to achieve the desirable therapeutic effects.

Example 7.

A beta-adrenergic agonist, for example salbutamol, can be given from a suppository dosage form to patients diagnosed with anal fissures or other anorectal disorders, either acute or chronic anal fissures from a topical dosage form, e.g. a cream. For suppository application, an approximate 300 mg to 3 gm of the suppository unit can be applied to the afflicted anorectal region using an application or by finger, one to four times daily. Once the suppository melted in the anal cavity, the salbutamol released from the dosage form is available to achieve the desirable therapeutic effects.

Example 8.

An α-adrenergic antagonist, i.e. scopolamine cab be applied from a topical spray to patients diagnosed with hemorrhoidal disorders, alone or in combination with a local anesthetic, for example, lidocaine. Scopolamine can be applied directly to the afflicted area with the propellant from the spray and can be used as needed to relieve the local pain and anal sphincter hypertonicity. Eventually, the application of scopolamine leads to healing of the hemorrhoidal disorders.

WHAT IS CLAIMED IS:

1. A composition for treating an anorectal disorder comprising a pharmaceutically acceptable carrier an amount of a spasmolytic agent effective to treat the anorectal disorder.

2. The composition of claim 1, wherein the spasmolytic agent comprises a beta-adrenergic agonist.

3. The composition of claim 1, wherein the spasmolytic agent comprises a cyclic nucleotide mimetic.

4. The composition of claim 1, wherein the spasmolytic agent comprises a phosphodiesterase inhibitor.

5. A method of treating an anorectal disorder, the method comprising administering to a subject in need of such treatment a therapeutically effective amount of a composition comprising a spasmolytic agent and a pharmaceutically acceptable carrier.

6. The method of claim 5, wherein the spasmolytic agent comprises a beta-adrenergic receptor agonist.

7. The method of claim 6, wherein the beta-adrenergic receptor agonist is isoproterenol.

8. The method of claim 6, wherein the beta-adrenergic receptor agonist is salbutamol.

9. The method of claim 5, wherein the spasmolytic agent comprises a non-specific or a specific phosphodiesterase inhibitor.

10. The method of claim 9, wherein the phosphodiesterase inhibitor is a non-specific phosphodiesterase inhibitor.

11. The method of claim 10, wherein the non-specific phosphodiesterase inhibitor comprises theophylline.

12. The method of claim 10, wherein the non-specific phosphodiesterase inhibitor comprises aminophylline.

13. The method of claim 9, wherein the phosphodiesterase inhibitor comprises a specific phosphodiesterase inhibitor.

14. The method of claim 13, wherein the specific phosphodiesterase inhibitor comprises a phosphodiesterase type V inhibitor.

15. The method of claim 13, wherein the specific phosphodiesterase inhibitor comprises sildenafil.

16. The method of claim 5, wherein the composition comprises a cyclic nucleotide mimetic.

17. The method of claim 16, wherein the cyclic nucleotide mimetic comprises a cyclic guanidine monophosphate analog.

18. The method of claim 17, wherein the cyclic nucleotide mimetic comprises a dibutyryl cyclic guanidine monophosphate.

19. The method of claim 16, wherein the cyclic nucleotide mimetic comprises a cyclic adenosine monophosphate analog.

20. The method of claim 19, wherein the cyclic adenosine monophosphate analog comprises dibutyryl cyclic adenosine monophosphate.

21. A composition comprising at least one alpha-adrenergic receptor antagonist, and a pharmaceutically acceptable carrier.

22. A method of treating an anorectal disorder, the method comprising administering to a subject in need of such treatment a therapeutically effective amount of a composition comprising an alpha-receptor antagonist, wherein said therapeutically effective amount increases or decreases hypertonicity of an anal sphincter muscle of the subject.

23. A composition comprising a nitric oxide donor, an agent which increases a level of a cyclic nucleotide in an anal sphincter muscle, and a pharmaceutically acceptable carrier.

24. A method of treating an anorectal disorder, the method comprising administering to a subject in need of such treatment a therapeutically effective amount of a composition comprising a potassium channel opener, wherein said therapeutically effective amount increases or decreases hypertonicity of an anal sphincter muscle of the subject.

25. The composition of claim 1, wherein the spasmolytic agent is present in the composition in an amount of from about 0.001% to about 15% by weight.

26. The composition of claim 23, wherein the nitric oxide donor is nitroglycerin.

27. The composition of claim 23, wherein the agent which increases a level of a cyclic nucleotide in an anal sphincter muscle is isoproterenol.

28. A method of treating an anorectal disorder, the method comprising administering to a subject in need of such treatment a therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier and an agent which increases a level of cyclic guanidine monophosphate or cyclic adenosine monophosphate in a tissue of an anal sphincter muscle of the subject, thereby increasing or decreasing hypertonicity of an anal sphincter muscle of the subject.

29. The method of claim 29, wherein the composition further comprises nitroglycerin.